CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20844, S001

MEDICAL REVIEW(S)

Ware

FEB 23 1999

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

REVIEW AND EVALUATION OF CLINICAL DATA

NDA (serial no.)	20,505 (001) and 20,844 (001)
SPONSOR	R. W. Johnson
DRUG (generic name)	Topamax (Topiramate)
INDICATION	Epilepsy
MATERIAL SUBMITTED	(1) Request for labeling change (#20,844) (2) Final Safety Update (#20,505)
CORRESPONDENCE DATE	1/29/99
DATE RECEIVED	2/1/99
DATE REVIEWED	2/23/99

I. INTRODUCTION

Topamax (TOP) was approved as adjunctive therapy to treat partial seizures in adults with epilepsy on 24 December 1997; an approvable letter was sent to the sponsor on 28 July 1998 for the supplemental indication of pediatric partial-onset seizures. The sponsor now submits:

(1) a request for labeling change to unify the labels for the tablet and sprinkles formulations into a single label (both the sprinkle and tablet formulations were found to be bioequivalent, the basis for the approval of Topamax sprinkles (see the review by Dr. Iftekar Mahmood); and

(2) A Final Safety Update, which encompasses the total pediatric clinical trials experience.

The Final Safety Update extends the date of the Four-Month Safety Update from 1 April 1998 to 1 August 1998, and reviews all deaths and serious adverse events encompassing all TOP clinical studies conducted under IND _____ between 1 October 1995 and 1 August 1998, as well as spontaneous adverse event reports from the date of first marketing (1 October 1995 in the United Kingdom) to the cutoff date of 1 August 1998. Much of this material has been extensively reviewed elsewhere; the information will not be repeated here. Only new data will be reviewed.

II. DEATHS

There were no new adult or pediatric death for the period 1 April 1998-1 August 1998. The SUDEP rate for TOP is given as 0.0036 death per patient-year in the Final Safety Update (v 4, p 131), but is presented as 0.0035 in current labeling, both calculated from data showing 10 unexplained deaths in a cohort of 2,796 patient-years.

III. SERIOUS ADVERSE EVENTS

PEDIATRIC

There were two cases of serious adverse events in the pediatric clinical trials during the period 1 October 1995 and 1 August 1998 (see v 4, p 62):

Randomized Dose Group: High-dose (200 or 500 mg/day TPM)

Subject 9030 (Protocol TOPMAT-EPMN- 104; dosage at onset of event: 200 mg/d [5.4 mg/kg per day]; limiting adverse event(s): arthralgia, autoantibody response hypertonia): This 12-year-old, 36.8 kg girl with idiopathic epilepsy was not receiving an AED at the time of randomization to high-dose (200 mg/day) topiramate therapy. During the titration period of the study, the subject experienced mild headache and gastrointestinal distress on Day 28, and moderate hyperkinesia and asthenia on Days 31 and 32, respectively. These events occurred at a topiramate dosage of 125 mg/day, were all considered possibly related to topiramate, and all resolved spontaneously while continuing therapy. The subject achieved her assigned dosage of 200 mg/day topiramate on Day 36. Mild constipation (Day 61) that was considered possibly related to topiramate and mild insomnia (Day 68) the was considered unlikely to be related to topiramate both resolved spontaneously constipation resolved in 15 days and insomnia resolved in 9 days. The subject had further mild symptoms including a stiff neck (hypertonia) on Day 307, bilateral knee pain (arthralgia) on Day 334, and joint pain of the wrists, elbows, and hip (arthralgia) on Day 355 Ibuprofen was administered for hypertonia and arthralgia, On Day 433, the subject had a antinuclear antibody (ANA) titer of 1:80. The investigator noted that the subject experience substantial weight loss (although not reported as an adverse event). During the double-blind phase of the trial, the subject's weight increased front 36.8 kg recorded at baseline to 40.3 (a 9.5% increase) on Day 183; thereafter, her weight was 39.1 kg on Day 349 and 42.5 kg Day 477. Topiramate therapy was discontinued due to joint pain and a positive ANA titre both considered possibly related to topiramate therapy, and due concern that these condition might have a negative effect on the subject's growth and rheumatologic condition. These adverse events persisted as of the subject's last visit in the clinical study database. Further information from the investigator indicate that the subject resumed normal growth a discontinuation of topiramate and that her arthralgia had resolved.

Subject 9372 (Protocol TOPMAT-EPMN-104; dosage at onset of event: 200 mg/da [7.6 mg/kg per day]; limiting adverse event(s): renal calculus): This 8-year-old, 26.4 boy with no known etiology of epilepsy was not receiving any AED during the baselin phase of the study. Other than epilepsy, the subject's medical history was unremarkable. The subject completed the titration period and achieved his assigned dosage of 200 mg/day o Day 36 of the double-blind phase. On Day 190, routine urinalysis revealed clinical significant hematuria (occult blood in the urine: 3+; RBCs in the urine: innumerable Ultrasound showed three kidney stones (renal calculi) in the left kidney. Renal calculi were considered by the investigator to be possibly related to topiramate and therapy discontinued. The subject's topiramate dosage was tapered over a 20-day period an carbamazepine therapy initiated to prevent breakthrough seizures. Urinalysis performed o Day 219, two days after complete discontinuation of topiramate, was negative for occ blood and no RBCs were seen upon microscopic examination. No further kidney problems were reported after discontinuation of topiramate.

In light of the above case, the labeling for treatment-emergent adverse events in the pediatric population should add appropriate COSTART terms -- if the events are found to occur at the appropriate frequency (>1% of the population under study) -- for kidney stones, arthralgia, positive ANA, impaired maturation, hypertonia.

ADULT

In the adult population, the following six new cases of serious adverse events occurred in clinical trials during the period 1 October 1995 and 1 August 1998 (see v 4, p 117):

Table 42: Adults With Serious Adverse Events'
(All Subjects in Study TPS TR)

Protocol Investigator/ Subject No.	Age Sex	Adverse Event(s)	Date of First TPM Dose	Date of AE Onset	Dosage at AE Onset (mg/day)	Relationship Outcome
Protocol TPS-TR - Open-Label Extension Phase						
03042	27 F	Unintended pregnancy	07 Feb 96	- - Jul 96	Unk.	Unlikely/NA
		Spontaneous abortion				Unlikely/NA
06073	27 F	Upper respiratory inf.	09 Jan 96	26 Dec 96	400	Unlikely/NR
09181	32 F	Uterine neoplasm	15 Aug 95	15 May 96	600	Unlikely/NR
		Uterine disorder NOS		15 May 96	600	Unlikely/NR
		Renal tubular disorder		16 May 96	600	Unlikely/NR
		Abnormal renal function		16 May 96	600	Unlikely/NR
		Vomiting		22 May 96	600	Unlikely/NR
12206 (resolved)	21 F	Therapeut. resp. inc.++ (study drug overdose)	08 Feb 96	28 Feb 97	800	Unlikely
		Somnolence		28 Feb 97	800	NR/NR
		Acidosis		28 Feb 97	800	NR/NR
		Hypokalemia		28 Feb 97	800	NR/NR
16211	32 F	Encephalopathy+	26 Mu 96	26 May 96	800	Likely/NR
		Anorexia		26 May 96	800	Likely/NR
		Weight decrease+	26 May 96		800	Likely/NR
16217	37 F	Osteomyelitis	21 Feb 96	- - Mu 97	200	Unlikely/NR

Includes serious adverse events (SAES) in Study TPS TR reported to the RWJPRI Global Safety and Pharmacovigilance Department after the 30 June 1996 cutoff for inclusion in the FSU to NDA 20-505 through the 1 August 1998 cutoff for this safety update. Based on investigator's assessment at the time of the occurrence of the adverse event; for relationship, probable = probable/likely
+An IND Safety Report was filed with FDA for this event.
++ Subject discontinued therapy due to this serious adverse event.

Key: NA=not applicable; NR=not reported

All of these adverse events have been reported in labeling for the adult population.

IV. ADVERSE EVENTS IN LABELING

No additional events need to included, and no changes made to the rates already found, in present labeling.

Following instructions from the Agency, the sponsor has omitted [redacted] from the list of treatment-emergent adverse events occurring in the pediatric population at the same rate on drug as on placebo.

V. POSTMARKETING EXPERIENCE

In my review of an Epidemiology consult, dated 6/25/98, I recommended that the following Postmarketing paragraph be included in labeling:

Postmarketing and Other Experience: *In addition to the adverse experiences reported during clinical testing of TOPAMAX, the following adverse experiences have been reported in patients receiving marketed TOPAMAX from worldwide use since approval. These adverse experiences have not been listed above and data are insufficient to support an estimate of their incidence or to establish causation. The listing is alphabetized: cholelithiasis, hepatic failure, hepatitis, pancreatitis, and renal tubular acidosis.*

One patient, a 30-40 year-old female on a stable dose of carbamazepine for over a year, was begun on Topamax at 50 mg/day, then subsequently titrated to 300 mg/day (over 4 months). During the titration period, her liver function tests rose 300-fold and she developed signs of hepatic encephalopathy and the hepatorenal syndrome, necessitating a liver transplant. Histopathology was "quite compatible with toxic influence."

In keeping with the above, the "Warnings" section should advise prudent monitoring of SGOT, SGPT, and bilirubin while patients are on TOPAMAX.

VI. CONCLUSION

I recommend approval of Topamax for the indication of pediatric partial-onset seizures. I also recommend unifying the labeling for Topamax tablets and sprinkles, as proposed by the sponsor, but with the following changes:

(a) above Postmarketing section should be included in the revised labeling, which has been provided by the sponsor;

(b) the "Warnings" section should advise prudent monitoring of liver function tests;

(c) to the list of treatment-emergent adverse events in the pediatric population, the sponsor should add COSTART terms for the following, if found to occur at the appropriate frequency (>1% of the population under study): kidney stones, arthralgia, positive ANA, impaired maturation, hypertonia.

VII. RECOMMENDATIONS

(1) Add Postmarketing section, as above.

(2) The "Warnings" section should advise prudent monitoring of liver function tests.

(3) Change the SUDEP rate in labeling to [redacted] to correspond with the rate given

in the Final Safety Update.

(4) To the list of treatment-emergent adverse events in the pediatric population, the sponsor should add COSTART terms for the following, if found to occur at the appropriate frequency (>1% of the population under study):

/S/

Richard M. Tresley MD
Medical Reviewer

NDA 20,505 (001) and 20,844 (001) Supplements div file/Katz R/Malandrucco M/Tresley R/2/23/99

APPEARS THIS WAY
ON ORIGINAL

COPY FOR YOUR INFORMATION

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

CLINICAL REVIEW OF NDA

NDA Number	20,505
Generic (Brand) Name	Topamax (topiramate)
Sponsor	RW Johnson Pharmaceutical Research Institute
Indication	1. sNDA: adjunctive treatment for (a) pediatric partial-onset seizures [redacted] (c) generalized tonic-clonic seizures 2. Four-Month Safety Update 3. 20 March 1998 Update 4. 28 April 1998 Additional Analyses
Classification	S
Correspondence Date	31 July 1997 (sNDA) 27 February 1998 (Four-Month Safety) 20 March 1998 (ISE Update) 28 April 1998 (Additional Analyses)
Original Receipt Date	1 August 1997 (sNDA) 2 March 1998 (Four-Month Safety) 23 March 1998 (ISE Update) 29 April 1998 (Additional Analyses)
Clinical Reviewer	Richard M. Tresley, MD
Review Completed	9 May 1998

CONTENTS

		PAGE
I.	INTRODUCTION	5
II.	EFFICACY	
	(a) Pediatric Partial-Onset Seizures (single trial, YP)	5
	Trial Design	
	Inclusion/Exclusion Criteria	
	Population	
	Withdrawals	
	Protocol Deviations	
	Dosage form	
	Outcome Measures	
	Compliance	
	Results	
	Secondary	
	Pharmacokinetic Data	
	Subgroup Analyses	
	(c) Generalized Tonic-Clonic Seizures (two trials, YTC and YTCE)	
	(1) Introduction	12
	(2) YTC	12
	Trial Design	
	Inclusion/Exclusion Criteria	
	Population	
	Withdrawals	
	Protocol Deviations	
	Dosage form	
	Outcome Measures	
	Compliance	

Results
Secondary
Pharmacokinetic Data
Subgroup Analyses

(3) YTCE 17
Trial Design
Inclusion/Exclusion Criteria
Population
Withdrawals
Protocol Deviations
Dosage form
Outcome Measures
Compliance
Results
Secondary
Pharmacokinetic Data
Subgroup Analyses

(4) Summary of PGTC Trials 21

III. SAFETY 27

Data Base (adult and pediatric)
Deaths
Serious Adverse Events
Withdrawals Due to Adverse Events
Treatment-Emergent Adverse Events
Overall Adverse Event Profile:
Safety Labs and Other Data
Global Evaluation of Mental Status

IV. DOSING RECOMMENDATIONS 42

V. CONCLUSION 42

VI. RECOMMENDATIONS 43

VII. TABLES 44

Study YP (vol 13/168) 45

Study YTC (vol 29/168) 56

Study YTCE (vol 39/168) 62

Integrated Summary of Efficacy (ISE; vol 53/158) 71

20 March 1998 Submission 78

APPEARS THIS WAY
ON ORIGINAL

I. INTRODUCTION

Topamax (TOP) was approved as adjunctive therapy to treat partial seizures in adults with epilepsy on December 24, 1997. The sponsor has submitted three supplemental NDAs to support indications for use, as an adjunctive agent, in the treatment of (1) pediatric partial-onset seizures (single controlled trial), (2) [redacted] and (3) primary generalized tonic-clonic seizures with or without other generalized seizure subtypes (two controlled trials). Each supplement will be discussed separately with respect to efficacy. A general safety assessment will be done for both pediatric and adult populations.

II. EFFICACY

(a) Pediatric Partial-Onset Seizures (Study YP)

TRIAL DESIGN: This Phase 3, multicenter (17 centers, 17 investigators), randomized, double-blind, placebo-controlled study was conducted in the United States and Costa Rica during the period 6/2/94-5/29/96. Its aim was to evaluate topiramate as adjunctive therapy in pediatric subjects with uncontrolled partial-onset seizures with or without secondary generalization. Four total daily (target) doses of topiramate were tested -- 125, 175, 225, and 400 mg/day -- based on subject weight to approximate 6 mg/kg/day.

The trial was divided into two phases (see Table 4 and Figure 2): baseline (56 days) and double-blind (112 days). During the baseline period, subjects received a constant dose of one or two anticonvulsants (AEDs), and the number and type of seizures were monitored on this regimen. Subjects met eligibility requirements for the double-blind portion if they had at least 6 partial-onset seizures during the 56 days, with at least one seizure per 28-day period. Those who were eligible were randomized in equal proportions at each center to placebo or topiramate arms while continuing their baseline AEDs.

The double-blind portion consisted of titration and stabilization phases, each 56 days in length. Study drug was titrated to the subject's assigned (target) dose or maximum tolerated dose in four 2-week intervals: during the first interval, the initial dose was 25 or 50 mg/day, based on weight and administered once in the evening; and, during subsequent intervals, the dosing interval was twice daily, titrated to maximum daily dosages of 125, 175, 225, and 400 mg/day based on weight (see Table 3 for dosing schedules). Target doses could be altered, depending on toleration; Table 22 lists treatment-emergent AEs necessitating dosage adjustments. Subjects then continued on this regimen for the 56 days of the stabilization period (see Table 19 for information about duration of the double-blind portion).

All patients completing the stabilization period were permitted to enter an open-label extension. Those who chose not to do so or discontinued prematurely had their study drug tapered off.

Three amendments to the original protocol were implemented: [redacted]

(2) dated 2 May 1995, after enrollment had reached about 39%: the use of centrally acting sympathomimetics and felbamate was added to the exclusion criteria;

(3) dated 13 July 1995, after enrollment had reached about 56%: the minimum eligibility age was modified from 4 years to 1, and the maximum age from 14 to 16 years; the sample size was decreased from 90 to 72 because of slow enrollment; and zonisamide was disallowed as a concomitant medication.

Another protocol change was implemented (though not as an amendment) when less than 10 subjects were enrolled, permitting subjects, who participated in the baseline period, to reduce

the duration of the baseline period if they were able to provide retrospective seizure information (based on a parent's or guardian's records) that totalled 56 days of seizure data when added to the prospective baseline experience.

INCLUSION/EXCLUSION CRITERIA: Males and females, aged 1-16; however, the youngest enrolled was 2 years old (two patients). Tables 1 and 2 delineate the inclusion/exclusion criteria.

POPULATION: Although the planned sample size was "approximately 72" subjects, 86 were eventually randomized (mean age: 10.6 years; age range: 2-16 years): 45 to placebo, 41 to topiramate. The sponsor explains (v 13, p 41) that there were already a number of potential subjects already screened for the study at the time the cohort approached 72 and the sponsor notified investigators to stop enrollment. "[I]t was considered unethical to disallow entry to those subjects" (v 13, p 41). All 86 subjects were included in the intent-to-treat analyses of safety and efficacy. Tables 6a and 6b display demographic and baseline characteristics.

With respect to demographic differences between treats and placebo, the mean was greater for the placebo group due to two patients with high baseline seizure rates, but the median baseline seizure rates were comparable: subject 45 (1,133/month) and subject 522 (271/month). Nevertheless, seizure types were similar in both groups. As for racial make-up, there were no blacks on placebo.

The profiles of concomitant medications appeared comparable between treatment groups. The most common non-anticonvulsants were analgesics, cough and cold preparations, vitamins, antibiotics, and nasal preparations (for a listing, see v 16, pp 1169-1234).

WITHDRAWALS: 83/86 subjects randomized to treatment completed double-blind therapy. The three withdrawals are shown on Table 7. Two patients were on placebo: one discontinued due to an adverse event (rash), and the second due to lack of patient cooperation. The single TOP dropout was a 5-year-old who failed two clinical visits during the trial but returned for his final appointment on Day 119, and who, moreover, was deemed noncompliant since he stopped taking study drug and had not maintained his seizure diary.

PROTOCOL DEVIATIONS: (1) 32 subjects (16 in each treatment group) were randomized to the double-blind phase before completing the protocol-specified 56-day baseline period; (2) 2 subjects (1 in each treatment group) weighed 15 kg and were allowed to enter baseline; (3) 6 placebo and 11 topiramate patients received more than 2 background AEDs at baseline; (4) 2 patients (1 in each treatment group) received a dosage of study drug exceeding the target daily dosage (the placebo patient, assigned to 125 mg/d, received 200 mg once during the study; the topiramate patient, assigned to 125 mg/d, received 250 mg once during the study; v 13, p 47).

DOSAGE FORM: TOP was supplied as 25-mg (Batches R4568, R5570) and 100-mg (Batches R5509, R5512) tablets. Maximum doses were based on subject weight: 125 mg/d (16-24.9 kg), 175 mg/d (25-33.9 kg), 225 mg/d (34-42.9 kg), and ≥400 mg/d (≥43 kg).

OUTCOME MEASURES:

PRIMARY: Percent reduction from baseline in the average monthly rate of partial-onset seizures during the double-blind portion of the trial. Seizures were coded by the International Classification of Epileptic Seizures (1981).

SECONDARY: (1) Percent reduction from baseline in the average monthly seizure rate for all seizures;
(2) percent reduction from baseline in the average monthly seizure rate for secondarily generalized seizures;
(3) percent treatment responders, defined as subjects with ≥50% reduction from baseline in the average months seizure rate;

(4) parental global evaluation of seizure severity.

PLANNED ANALYSES: The cohort was established at 72 (but see above). A sample size of 36 subjects in each treatment group was estimated to be adequate with 80% power to detect a between-group difference of 40% in percent reduction in the partial-onset seizure rate (see v 14, pp 36-7). This assumed a Type I error level of 5% and a population standard deviation of 60%.

According to the study protocol, "The primary efficacy parameter will be percent reduction from baseline seizure rate based on partial-onset seizures [for the double-blind phase of the study].

"Group differences in percent reduction from baseline partial-onset seizure rate will be analyzed using 2-way (with treatment and investigator as factors) analysis of variance. Group differences in responders will be analyzed using logistic regression methodology. Treatment by investigator interactions will be assessed and explored further if the p-value is ≤ 0.10. Parental/guardian global evaluation will be analyzed using Mantel-Haenszel methodology. Percent reduction from baseline seizure rate based on all seizures will be analyzed descriptively as a secondary parameter" (v 14, p 455).

PERFORMED ANALYSES: Primary analyses included all randomized subjects (ITT) during the double-blind phase (titration and stabilization periods) up to study drug discontinuation. Secondary analyses using only stabilization period data (beginning on Day 57 of the double-blind phase), employed identical statistical methods. Average monthly (28-day) seizure rates were computed for the baseline and double-blind phases. A 2-way analysis of variance on ranks (with treatment and center as factors), by means of SAS for general linear model, was chosen to analyze group differences in percent reduction from baseline seizure rate.

Centers with low enrollment ($n<6$) were pooled and included as single centers, not exceeding the size of the largest center ($n=12$). The algorithm ranked all centers in order of total sample size and then alphabetically within sample size.

For those subjects experiencing secondarily generalized seizures at baseline or during the double-blind phase, percent reduction from baseline in generalized seizures only was computed. However, if secondarily generalized seizures were absent during baseline but present during the double-blind phase, a baseline seizure rate of 0.001 per month was assigned to allow calculation of seizure-rate reduction.

Additionally, treatment groups were compared to derive the percent treatment responders for partial-onset and all seizures, using the Cochran-Mantel-Haenszel method stratified by center.

Parental global evaluation of improvement in seizure severity was analyzed by exact Wilcoxen rank-sum test unstratified and stratified by center (via StatXact).

All statistical tests were two-sided at alpha=0.05, except for interaction in the linear model, which was at the 0.10 level.

COMPLIANCE: Compliance appears to have been good, as determined by the maintenance of reasonably constant plasma concentrations of topiramate and concomitant AEDs throughout the stabilization period of the trial (see v 13, p 64; TOP concentrations are shown in v 16, pp 1095-1103, and concentrations of concomitant AEDs in v 16, pp 1125-60).

RESULTS: All 86 patients (45 placebo; 41 TOP) who entered the double-blind trial were included in the efficacy analyses (ITT). Seizure data for the three withdrawals were averaged for that portion of the double-blind phase completed up to the time study drug was discontinued; Table 19 shows the duration of the time spent in the double-blind phase for all randomized subjects. The ITT analyses included all seizure data for both partial-onset and all seizures (see Table 14). Note that two topiramate and no placebo patients were seizure free during the double-blind portion.

The primary outcome measure was the percent reduction from baseline in the average monthly partial-onset seizure rate during the double-blind phase. Table 8 shows a median percent reduction of 33.1% for the topiramate group versus 10.5% for the placebo group, yielding a statistically significant difference in favor of treatment ($p=0.034$).

With respect to secondary outcome measures, TOP patients demonstrated a median percent reduction in secondarily generalized seizures of 31.6% versus an increase of 10.6% in the placebo group. 21/24 (88%) TOP and 25/28 (89%) placebo patients who reported no secondarily generalized seizures at baseline did not exhibit this type of seizure activity during the double-blind phase. The median percent reduction from baseline for all seizures was 31.9% for TOP and 10.5% for placebo patients (p=0.077).

There were no statistically significant treatment-by-center interactions with respect to partial-onset seizures (p=0.159) or all seizures (p=0.252). Figure 3 displays the data graphically, illustrating results favorable to TOP in 7 of the 9 centers.

Treatment responders were defined as patients with ≥50% reduction from baseline seizure rates during the double-blind phase. Table 9 shows that (1) 39% TOP, as opposed to 20% placebo, subjects were treatment responders with respect to partial-onset seizure (p=0.080); (2) 39% TOP, compared to 22%, patients were treatment responders based on all seizures (p=0.127); and 45% TOP, versus 30% placebo, subjects were treatment responders for the category of secondarily generalized seizures. There were no statistically significant treatment-by-center interactions with respect to partial-onset seizures (p=0.120) or all seizures (p=0.206). In contrast (see Table 10), a statistically significant number of TOP, versus placebo, patients experienced ≥75% reduction in seizure rate with respect to both partial-onset seizures (17% to 2%; p=0.019) and all seizures (17% to 2%; p=0.019). For secondarily generalized seizures, the figures were 25% TOP vs 15% placebo patients.

Finally, for the parental global evaluation of improvement in seizure severity (Table 11), 59% TOP vs 33% placebo patients showed improvement (minimal, moderate, or marked). The figures for marked improvement were statistically significant (p=0.025) in favor of TOP (29%), compared to placebo (11%).

The review of Dr. Sue-Jane Wang (FDA Biostatistics) concurs with the above.

PHARMACOKINETIC DATA: The mean plasma concentration of TOP for the entire double-blind phase of the trial was 3.6 (±1.89 SD) ug/ml (v 13, p 47). Changes in plasma concentration for concomitant AEDs were insignificant (see Table 12). Of those who achieved their target dosage at some time during the trial, 38 (93%) were in the placebo and 42 (93%) in the TOP groups (Tables 15, 16, 17). 40 (89%) placebo and 31 (76%) TOP patients achieved their target dosage and completed the stabilization period at that dosage (Table 18).

Median percent reduction and percent treatment responders (≥50% reduction in seizure rate) were greatest in the mid-range plasma TOP concentration, 3.2-5.4 ug/ml, for both partial-onset and all seizures (see Table 13). No significant correlation (v 13, p 59) was observed between plasma TOP concentration and percent reduction in the average monthly partial-onset (p =0.536) or all seizure rates (p=0.452).

SUBGROUP ANALYSES: The ratio of male-to-female representation was relatively close (male:female::14:11 in both the drug-treated and placebo groups; see the demographics in Table 6b). the crude percentage rates shown in Attachment 2.1.4, which compares the two groups in terms of median seizure reduction, would lead to the conclusion that both did well on TOP. No differences with regard to effectiveness or safety issues were noted for gender, according to a phone conversation with the sponsor on 2/10/98 (Catherine Glenkowski , covering for Michael Kaufman, Joe Ward [medical writer], and Judy Smith [statistician]).

Racial representation was sparse, and no conclusions can therefore be reached about the effect of topiramate on groups other than whites. Only 4 (4/41) blacks and 1 (1/41) Oriental were randomized to study drug; in the placebo group, there were no blacks and 2 Orientals.

4 pages REDACTED

TRADE SECRET/

CONFIDENTIAL
COMMERCIAL
INFORMATION

(c) Generalized Tonic-Clonic Seizures

(1) Introduction

Two multicenter, randomized, double-blind, placebo-controlled studies (identical design) were conducted (YTC with 18 sites in the US and Costa Rica, YTCE with 16 sites in the US and Europe), to evaluate TOP in the treatment of uncontrolled primary generalized tonic-clonic seizures (tonic-clonic seizures considered to be generalized from the onset) with or without other generalized seizures subtypes (hereafter referred to as PGTC seizures).

(2) YTC

TRIAL DESIGN: This Phase 3, multicenter (18 centers, 18 investigators), randomized, double-blind, placebo-controlled study was conducted in the United States (17 sites) and Costa Rica (1 site) during the period 5/4/94-7/5/96. Its aim was to evaluate topiramate as adjunctive therapy in subjects with uncontrolled primary generalized tonic-clonic seizures with or without other generalized seizure subtypes. Maximum total daily (target) doses of TOP, based on subject weight, were 175 mg/day (25-33.9 kg), 225 mg/day (34-42.9 kg), and 400 mg/day (≥43 kg), to approximate 6 mg/kg/day (theoretical range: <9.3 mg/kg/d).

The trial was divided into two phases (see Figure 1): baseline (56 days) and double-blind (140 days). During the baseline period, subjects received a constant dose of one or two anticonvulsants (AEDs), and the number and type of seizures were monitored on this regimen. Subjects met eligibility requirements for the double-blind portion if they had ≥3 PGTC seizures during the 56 days (at least one during each 28-day period), with at least one seizure per 28-day period. Those who were eligible were randomized in equal proportions at each center to placebo or topiramate arms while continuing their baseline AEDs.

The double-blind portion consisted of two phases: titration (56 days) and stabilization (84 days). Study drug was titrated to the subject's assigned (target) dose or maximum tolerated dose as follows: during the first 28 days, TOP dosing was instituted as a single evening 50 mg dose, and thereafter increased to maximum daily dosages in two divided doses (see Table 3 for dosing schedules; Table 4 for a schedule of trial procedures). Target doses could be altered, depending on toleration; Tables 20 and 21 lists treatment-emergent AEs necessitating dosage adjustments. Subjects then continued on this regimen for the 84 days of the stabilization period (see Tables 15a, 15b, and 16 for dosage data during the double-blind and stabilization periods; Table 17 provides information about the duration of the double-blind portion).

All patients completing the stabilization period were permitted to enter an open-label extension. Those who chose not to do so or discontinued prematurely had their study drug tapered off.

No formal protocol amendments were made. However, a change in trial conduct was implemented to increase enrollment, permitting subjects to reduce the duration of the baseline phase if they could provide seizure information (based on personal records) that totaled 56 days of seizure information (*retrospective* seizure data) when added to their prospective baseline experience (*prospective* seizure data). This change affected 20 subjects (10 placebo, 10 TOP).

INCLUSION/EXCLUSION CRITERIA: Males and females, ≥4 years of age, weight >25 kg. Tables 1 and 2 delineate the inclusion/exclusion criteria.

POPULATION: 103 subjects were enrolled in the baseline phase, of whom 80 were randomly assigned to treatment (n_{TOP}=39; $n_{placebo}$=41). and included in the ITT analysis. Included among 39 TOP patients were 8, and among 41 placebo patients 13, pediatric subjects (aged 2-16).

With respect to the 23 subjects who were enrolled but not randomized, 9 were found ineligible during the baseline phase (8 due to an inadequate number of seizures; 1, AED medication change) and 13 were administrative exclusions (2 due to low body weight; 1, diagnosis of partial-onset seizures; 1, renal calculi history and unstable diabetes; 2, noncompliance; 1, history of brain abscess; 1, history of suicide attempt; 2 by subject choice; and 3 for reasons unspecified. See v 29/168, p 95).

Planned duration of the double-blind phase was 140 days, and the median duration for the two treatment groups was 142 days for TOP and 141 for placebo (see Table 17).

Tables 6a and 6b display demographic and baseline characteristics. Differences between treats and placebo included: (1) median body weight, according to which TOP patients were 10 kg heavier than placebo; and (2) the *mean/SD* and *range* for the category of all seizures, which show an imbalance between groups due to a single outlier with an average monthly seizure rate exceeding 79,000 (a figure difficult to believe), but the *medians* were very similar. Over 66% of randomized subjects had generalized tonic-clonic seizures, in addition to one or more other generalized seizures types. Rates for individual seizures types were similar between the two

groups.

Males and females were adequately represented, in terms of percentages, in both groups. As for racial make-up, there were small numbers of blacks (6 treats and 5 placebo) and only 1 representative from "other" racial groups (in the TOP arm).

The profiles of concomitant medications appeared fairly comparable between treatment arms. The most common non-anticonvulsants among placebo subjects were analgesics, antibiotics, nasal preparations, and vitamins; (v 33/168; pp 1180-1250).

WITHDRAWALS: Figure 2 provides a study completion and withdrawal summary for the randomized double-blind trial phase; Table 7 categorizes the dropouts. 72/80 randomized subjects completed double-blind therapy: 3 placebo and 5 TOP subjects prematurely dropped out (subject choice: 1 placebo, 2 TOP; limiting adverse event: 1 in each group; lost to follow-up: 1 placebo; and other: 2 TOP). Of these, 1 placebo and 2 TOP subjects completed all clinical visits and were therefore deemed to have completed the trial per protocol. Individual reasons for premature withdrawal are shown in Table 8.

PROTOCOL DEVIATIONS: 46 subjects (20 placebo, 24 TOP) had protocol deviations. 20 (10 placebo, 10 TOP) were randomized prior to completing the 56-day baseline phase. 21 (10 placebo, 11 TOP) were randomized, despite maintenance on more than two concomitant AEDs. In addition, 1 TOP subject was discontinued due to noncompliance with study drug and concomitant AED; 1 TOP subject prematurely advanced to the open-label extension because of a pharmacist's error in dispensing medication; and 1 TOP subject experienced complex partial seizures during the baseline phase and was subsequently randomized to the double-blind phase.

DOSAGE FORM: TOP was supplied as 25-mg (batch R5489) and 100-mg (batch R5509) tablets. Maximum doses, based on subject weight, were 175 mg/day (25-33.9 kg), 225 mg/day (34-42.9 kg), and 400 mg/day (≥43 kg), to achieve a total daily (target) dosage of 6 mg/kg/d, administered bid in equal doses.

OUTCOME MEASURES:

PRIMARY: "percent change in PGTC seizures during the double-blind phase as compare to the baseline phase. The study will be considered positive if the PGTC seizure rate has decreased significantly compared to placebo during the double-blind phase" (v 41/168, p 576).

SECONDARY: (1) Percent reduction from baseline in average monthly seizure rate during the double-blind phase for all seizures.

(2) Percent treatment responders for PGTC seizures, defined ≥50% reduction in baseline seizure rate during the double-blind phase.

(3) Global evaluation of seizure severity, completed by the subject or caregiver and assessing improvement in seizure severity at the end of the double-blind phase compared to the beginning of the titration period.

PLANNED ANALYSIS: Sample size was estimated by reference to percent reduction in seizure rates. The sample size needed in each group to detect a 30% difference in percent reduction in PGTC seizure rates from baseline between the two groups was calculated to be about 36 (total study population: 72), given a Type I error level of 5%, a power of 80%, two-sided test, and a population standard deviation of 45%.

Group differences in percent reduction in seizure rate from baseline, according to protocol, were to be examined using a two-way analysis of variance, with treatment and investigator as factors. Seizure rates, based on all seizures, were to be summarized by treatment groups. Group differences in responders, based on PGTC seizures, were to be analyzed using logistic regression methods. Treatment by investigator interactions were to be assessed further if the p-value were less than 0.10. Caregiver global evaluations were to be analyzed by means of Mantel-Haenszel

methodology. Demographic, laboratory, vitals, EKG, and adverse event data were to be summarized descriptively (see v 31/168, pp 27-28).

PERFORMED ANALYSIS: The primary efficacy analysis included the ITT population of all randomized subjects and used data from baseline and double-blind phases (both titration and stabilization periods) up to study drug discontinuation. Secondary analyses used data only from the stabilization period (beginning on Day 57 of the double-blind phase) but employed identical methodologies.

The average monthly (28-day) seizure rates were computed for both the baseline and double-blind phases and calculated as 28 times the total number of seizures reported during the period divided by the total number of days in the period. The double-blind phase seizure rate was defined, for each subject, as the average seizure rate over the entire double-blind phase. The percent reduction in PGTC seizure rate was defined as 100(B-D)/B, where B represents the baseline PGTC seizure rate and D the double-blind PGTC seizure rate. A two-way analysis of variance on ranks (with treatment and center as factors) was used to evaluate treatment group differences in percent reduction from baseline seizure rate. SAS procedure for General Linear Model was used in this analysis. Percent reduction in seizure rate was similarly analyzed for all seizures.

Centers with low enrollment (≤6 subjects) were pooled and included as single analysis centers, with each analysis center not exceeding the size of the largest center (13). The algorithm ranked all centers in order of total sample size and then alphabetically within sample size.

An additional secondary efficacy assessment compared treatment groups with respect to percent of PGTC responders (defined as ≥50% reduction in PGTC seizures), stratified by center, using the Cochran-Mantel-Haenszel method. This analysis was also performed based on all seizures.

Global evaluation of improvement in seizure severity was analyzed by exact Wilcoxen rank-sum test, unstratified and stratified by center, employing StatXact.

All statistical tests were two-sided. The significance levels employed for evaluating the effects of the covariate and the interaction term were 0.05 and 0.10, respectively.

COMPLIANCE: Plasma concentrations of TOP and concomitant AEDs were considered to be the most reliable indicators of compliance. According to the sponsor, these were "reasonably constant . . . throughout the maintenance period of the study" (v 32/168, p 48; for details, see v 43/168 pp 1114-19 [Appendix 3.3.4 for TOP concentrations] and v 33/168 pp 1147-76 [Appendix 3.4.2 for concomitant AED concentrations]).

RESULTS: 103 subjects were enrolled in the baseline phase, of whom 80 were randomly assigned to treatment (n_{TOP}=39; $n_{placebo}$=41) and included in the ITT analysis. Planned sample size in the initial protocol had been 36 per treatment group, which was estimated to be adequate to detect a 30% between-group difference in PGTC seizure rate, given assumptions of a 5% Type I error level, 80% power, and 45% population standard deviation.

Of the 80 subjects entering the double-blind phase (41 randomized to placebo, 39 to TOP), one placebo subject (number 161) had no PGTC seizures during baseline or the double-blind phase and was therefore omitted in the intent-to-treat efficacy analysis for variables based on PGTC seizures; given the definition of percent reduction in PGTC seizure rate (100[B-D]/B, where in this case B=0; see above), he could not mathematically be assigned a value. For all other efficacy variables, however, all 80 subjects were included in the ITT analyses. With regard to the 8 premature withdrawals (see Table 8), seizure data were averaged for that portion of the double-blind phase completed up to the time study treatment was discontinued.

ITT analyses include PGTC seizures and all seizures from the prospective portion of the baseline phase (up to 8 weeks) and the entire double-blind phase of the study (or up to study drug discontinuation for premature withdrawals). Efficacy analyses were conducted using only data from the stabilization period. Additional efficacy analyses of the entire double-blind phase and

stabilization period were also conducted using all baseline seizure data (retrospective and prospective seizure data), and including seizures recorded after study treatment discontinuation. According to the sponsor, the results of all efficacy analyses for the stabilization period were similar overall to those for the double-blind phase; also similar were the results when seizures recorded after therapy discontinuation, as well as when retrospective baseline date, were included.

As to the primary efficacy variable (see Tables 9, 10b, and 14 for tabulated results; Figure 4, for Kaplan-Meier curves), the percent reduction from baseline in the average monthly PGTC seizure rate during the double-blind phase, TOP subject experienced a median percent reduction of 56.7%, vs 9.0% for placebo, a statistically significant result in favor of TOP (p=0.019).

Statistical significance favoring TOP was also seen for the secondary efficacy endpoint of median percent reduction from baseline for all seizures during the double-blind phase: TOP subjects experienced a median percent reduction of 42.1%, compared to 9.0% for placebo (p=0.003).

The relative treatment differences was consistent across all centers (see Figure 3). No treatment-by-center interactions were detected between placebo and TOP groups with respect to PGTC seizures (p=0.796) or all seizures (p=0.584).

Other secondary efficacy categories were treatment responders and the global evaluation of improvement in seizure severity. With respect to treatment responders, defined as ≥50% reduction from baseline in seizure rate during the double-blind phase, 56% TOP subjects vs 20% placebo could be classified as responders for PGTC seizures (p=0.001), and 46% TOP subjects vs 17% placebo as responders for all seizures (p≤0.003). Both results were statistically significant in favor of treatment (see Table 10a). No treatment-by-center interactions were detected between placebo and TOP groups with respect to PGTC or all seizures (p≥0.677). If treatment response is defined as ≥75% seizure rate reduction (not a protocol-defined secondary outcome measure), 33% TOP vs 13% placebo subjects were responders for PGTC seizures (p=0.037), and 26% TOP vs 7% placebo subjects were responders for all seizures (p=0.026). Again, both are statistically significant in favor of treatment.

With regard to the subject's global evaluation of seizure severity, 62% TOP vs 56% placebo subjects showed a subjective improvement (minimal, moderate, or marked), which was not statistically significant (p=0.490). Nevertheless, more TOP subjects classified their improvement as marked (21% vs 7% for placebo; see Table 11).

During the double-blind phase, 13% TOP vs 5% placebo remained free of PGTC seizures (p=0.225), and 5% TOP vs 0% placebo subjects free of all seizures (p=0.173) -- both categories (not protocol-defined endpoints), while not statistically significant, demonstrated a numerical trend in favor of TOP.

Although other seizure types -- except for absence and tonic -- were not adequately represented (see Table 6b), median percent reduction from baseline in average monthly seizure rate numerically favored TOP over placebo for absence (53% vs 4%), myoclonic (52% vs an increase of 40%), and tonic (28% vs an increase of 1%).

PHARMACOKINETIC DATA: Median average dosage during the double-blind phase (titration and stabilization) was 3.7 mg/kg/day for TOP subjects, and during the stabilization period 5.1 mg/kg/day. 36 (88%) placebo and 36 (92%) TOP subjects achieved their target dosage at some point in the study (see Tables 15a and 15b); 34 (83%) placebo and 30 (77%) TOP subjects completed stabilization at that dosage (see Table 16).

The mean TOP plasma concentration over the entire double-blind period (titration and stabilization) was 5.1 ug/ml (v 29/168, p 49). Efficacy results within the two higher concentration strata were similar and exceeded those in the lowest concentration stratum (see Table 13).

A mean decrease in the plasma concentration of carbamazepine (-1.4 ug/ml) was noted and is, according to the sponsor, "not in a direction that would be expected to favor TOP in treatment comparisons" (v 29/168, p 60). Mean changes from baseline in plasma concentrations of other concomitant AEDs were small and not statistically significant between TOP and placebo patients (see Table 12).

SUBGROUP ANALYSES: The ratio of male-to-female representation was relatively close in both the drug-treated and placebo groups; see the demographics in Table 6b. Crude percentage rates were not provided in the NDA comparing the two groups in terms of median seizure reduction. However, no differences with regard to effectiveness or safety issues were noted for gender, according to a phone conversation with the sponsor on 2/10/98 (Catherine Glenkowski , covering for Michael Kaufman, Joe Ward [medical writer], and Judy Smith [statistician]).

Racial representation was sparse, and no conclusions can therefore be reached about the effect of topiramate on groups other than whites.

When the pediatric populations of both YTC and YTCE were pooled, the number of patients provided a large enough subgroup to evaluate. The results are noted in the Summary below.

(3) YTCE

TRIAL DESIGN: This Phase 3, multicenter (16 centers, 16 investigators), randomized, double-blind, placebo-controlled study was conducted in the United States (six sites, 31 subjects) and Europe (10 sites, 49 subjects) during the period 9/15/94-11/12/96. Its aim was to evaluate TOP as adjunctive therapy in subjects with uncontrolled primary generalized tonic-clonic seizures with or without other generalized seizure subtypes. Maximum total daily (target) doses of TOP, based on subject weight, were 175 mg/day (25-33.9 kg), 225 mg/day (34-42.9 kg), and 400 mg/day (≥43 kg), to approximate 6 mg/kg/day (theoretical range: <9.3 mg/kg/d).

The trial was divided into two phases (see Figure 1 and Table 4): baseline (56 days) and double-blind (140 days). During the baseline period, subjects received a constant dose of one or two anticonvulsants (AEDs), and the number and type of seizures were monitored on this regimen. Subjects met eligibility requirements for the double-blind portion if they had ≥3 PGTC seizures during the 56 days (at least one during each 28-day period), with at least one seizure per 28-day period. Those who were eligible were randomized in equal proportions at each center to placebo or TOP arms while continuing their baseline AEDs.

The double-blind portion consisted of two phases: titration (56 days) and stabilization (84 days). Study drug was titrated to the subject's assigned (target) dose or maximum tolerated dose as follows: during the first 28 days, TOP dosing was instituted as a single 50 mg evening dose, and thereafter increased to maximum daily dosages in two divided doses (see Table 3 for dosing schedules). Target doses could be altered, depending on toleration; Table 21 lists treatment-emergent AEs necessitating dosage adjustments and Table 20 reasons for study drug discontinuation. Subjects then continued on this regimen for the 84 days of the stabilization period (see Table 17 for information about duration of the double-blind portion).

All patients completing the stabilization period were permitted to enter an open-label extension. Those who chose not to do so or discontinued prematurely had their study drug tapered off.

No formal protocol amendments were made. However, a change in trial conduct was implemented to increase enrollment, permitting subjects to reduce the duration of the baseline phase if they could provide seizure information (based on personal records) that totaled 56 days of seizure information (*retrospective* seizure data) when added to their prospective baseline experience (*prospective* seizure data). This change affected 26 subjects (15 placebo, 11 TOP).

INCLUSION/EXCLUSION CRITERIA: Males and females, ≥4 years of age, weight >25 kg. Tables 1 and 2 delineate the inclusion/exclusion criteria.

POPULATION: 87 subjects were enrolled in the baseline phase, 80 of whom were randomly assigned to treatment (n_{TOP}=40; $n_{placebo}$=40). Included among the 40 TOP patients were 9, and among the 40 placebo patients 2, pediatric subjects (aged 2-16).

With respect to the 7 subjects who were enrolled but not randomized, 4 were found

ineligible during the baseline phase (less than 3 PGTC seizures) and 3 were administrative exclusions (1 screening failure (reason?); 1 failed to attend Visit 3 and did not take study treatments; 1 not randomized "due to some misunderstanding"; see v 39/168, p 111).

Planned duration of the double-blind phase was 140 days, and the median duration for each of the two treatment groups was 141 days. 77% of subjects had greater than 19 weeks (133 days) of double-blind treatment (see Table 17).

Tables 6a and 6b display demographic and baseline characteristics. There was one notable demographic imbalance between treats and placebo: the rate of baseline PGTC seizures and all seizures was higher in the TOP group. This problem is discussed at length in the Results section below. There were similar rates for most seizure types, except for atypical absence which was higher in the TOP group.

Males and females were adequately represented, in terms of percentages, in both groups. As for racial make-up, there were insignificant numbers of blacks (only 1 in the TOP group) and no representatives from other racial groups in either treatment arm.

The profiles of concomitant medications appeared fairly comparable between treatment arms. The most common non-anticonvulsants among placebo subjects were analgesics (acetaminophen [13 subjects], ibuprofen [4]); among TOP, analgesics (acetaminophen [5]), vitamins (5), and medroxyprogesterone acetate (4); (v 43/168, pp 1236-1306).

WITHDRAWALS: 60/80 subjects randomized to treatment completed the double-blind phase. Premature discontinuations numbered 11 in the placebo and 9 in the TOP group. Of these, 12 (7 placebo, 5 TOP) discontinued due to limiting adverse events, and 1 placebo subject died suddenly during the study (SUDEP). Table 8 delineates the reasons for withdrawal.

PROTOCOL DEVIATIONS: 31 subjects (16 placebo, 15 TOP) had deviations from the inclusion/exclusion criteria. 26 (15 placebo, 11 TOP) were randomized prior to completing the 56-day baseline phase. 8 (4 placebo, 4 TOP) were randomized, despite maintenance on more than two concomitant AEDs; and 2 in the TOP group, even though they had recently completed another experimental drug regimen (nitrazepam and clobazam). 1 TOP subject (number 39) was randomized to treatment even though he had no PGTC seizures during baseline; and 1 placebo subject, despite a history of attempted suicide. Incorrect dose treatments were found among 5 TOP subjects: 3 were assigned to a target dose of 400 mg/day, though their weights were 28.2, 41.4, and 28.2 kg; 2 took an overdosage (800 mg/day for 84.2 kg body weight, 1,200 mg/day for 84.9 kg).

DOSAGE FORM: TOP was supplied as 25-mg (US: batch R4993; Europe: batches 911 301, 913 410) and 100-mg (US: batch R6147; Europe: batches 909 301, 916 410, 917 410) tablets. Maximum doses, based on subject weight, were 175 mg/day (25-33.9 kg), 225 mg/day (34-42.9 kg), and 400 mg/day (≥43 kg), to achieve a total daily (target) dosage of 6 mg/kg/d, administered bid in equal doses.

OUTCOME MEASURES:

PRIMARY: "Percent change in PGTC seizures during the double-blind phase as compared to the baseline phase. The study will be considered positive if the PGTC seizure rate has decreased significantly compared to placebo during the double-blind phase" (v 41/168, p 576).

SECONDARY: (1) Percent reduction from baseline in average monthly seizure rate during the double-blind phase for all seizures.

(2) Percent treatment responders for PGTC seizures, defined as ≥50% reduction in baseline seizure rate during the double-blind phase.

(3) Global evaluation of seizure severity, completed by the subject or caregiver and assessing improvement in seizure severity at the end of the double-blind phase compared to the beginning of the titration period.

PLANNED ANALYSIS: Sample size was estimated by reference to percent reduction in seizure rates. The sample size needed in each group to detect a 30% difference in percent reduction in PGTC seizure rates from baseline between the two groups was calculated to be about 36 (total study population: 72), given a Type I error level of 5%, a power of 80%, two-sided test, and a population standard deviation of 45%.

Group differences in percent reduction in seizure rate from baseline, according to protocol, were to be examined using a two-way analysis of variance, with treatment and investigator as factors. Seizure rates, based on all seizures, were to be summarized by treatment groups. Group differences in responders, based on PGTC seizures, were to be analyzed using logistic regression methods. Treatment by investigator interactions were to be assessed further if the p-value were less than 0.10. Caregiver global evaluations were to be analyzed by means of Mantel-Haenszel methodology. Demographic, laboratory, vitals, EKG, and adverse event data were to be summarized descriptively (see v 41/168, p 584).

PERFORMED ANALYSIS: The primary efficacy analysis included the ITT population of all randomized subjects and used data from baseline and double-blind phases (both titration and stabilization periods) up to study drug discontinuation. Secondary analyses used data only from the stabilization period (beginning on Day 57 of the double-blind phase) but employed identical statistical methodologies.

The average monthly (28-day) seizure rates were computed for both the baseline and double-blind phases and calculated as 28 times the total number of seizures reported during the period divided by the total number of days in the period. The double-blind phase seizure rate was defined, for each subject, as the average seizure rate over the entire double-blind phase. The percent reduction in PGTC seizure rate was defined as 100(B-D)/B, where B represents the baseline PGTC seizure rate and D the double-blind PGTC seizure rate. A two-way analysis of variance on ranks (with treatment, center, and baseline PGTC seizure rate as factors) was used to evaluate treatment group differences in percent reduction from baseline seizure rate. SAS procedure for General Linear Model was used in this analysis. Percent reduction in seizure rate was similarly analyzed for all seizures.

Centers with low enrollment ($\leq$6 subjects) were pooled and included as single analysis centers, with each analysis center not exceeding the size of the largest center (13). The algorithm ranked all centers in order of total sample size and then alphabetically within sample size.

An additional secondary efficacy assessment compared treatment groups with respect to percent PGTC responders (defined as $\geq$50% reduction in PGTC seizures), stratified by center and using the Cochran-Mantel-Haenszel method. This analysis was also performed based on all seizures.

Global evaluation of improvement in seizure severity was analyzed by exact Wilcoxen rank-sum test, unstratified and stratified by center, employing StatXact.

All statistical tests were two-sided. The significance levels employed for evaluating the effects of the covariate and the interaction term were 0.05 and 0.10, respectively.

COMPLIANCE: Plasma concentrations of TOP and concomitant AEDs were considered to be the most reliable indicators of compliance. According to the sponsor, these were "reasonably constant . . . throughout the maintenance period of the study" (v 39/168, p 51; for details, see v 43/168 pp 1194-98 [Appendix 3.3.4 for TOP concentrations] and pp 1212-32 [Appendix 3.4.2 for concomitant AED concentrations]).

RESULTS: 80 subjects entered the double-blind phase, 40 randomized to placebo and 40 to TOP. The ITT population, accepted for the purpose of analysis for variables based on PGTC seizures, consisted of 40 placebo and 39 TOP subjects. One TOP subject (number 39) had no PGTC seizures during baseline or the double-blind phase and was therefore omitted; given the definition of percent reduction in PGTC seizure rate (100[B-D]/B, where in this case B=0; see above), he

could not mathematically be assigned a value. For all other efficacy variables, however, all 80 subjects were included in the ITT analyses. With regard to the 20 premature withdrawals, seizure data were averaged for that portion of the double-blind phase completed up to the time study treatment was discontinued.

ITT analyses include PGTC seizures and all seizures from the prospective portion of the baseline phase (up to 8 weeks) and the entire double-blind phase of the study (or up to study drug discontinuation for premature withdrawals). Efficacy analyses were conducted using only data from the stabilization period. Additional efficacy analyses of the entire double-blind phase and stabilization period were also conducted using all baseline seizure data (retrospective and prospective seizure data), and including seizures recorded after study treatment discontinuation. According to the sponsor, the results of all efficacy analyses for the stabilization period were similar overall to those for the double-blind phase; also similar were the results when seizures recorded after therapy discontinuation, as well as when retrospective baseline date, were included.

With regard to the primary efficacy variable (percent reduction from baseline in average monthly PGTC seizure rate during the double-blind phase), TOP subjects experienced a 57.1% median percent reduction, compared to 33.2% for the placebo group (see Tables 9 and 10a, as well as Figure 4 for Kaplan-Meier graphs). Although the difference numerically favored TOP, the result was not statistically significant (p=0.124). The TOP group also had a greater median percent reduction from baseline for all seizures, 26% compared to 12.1% for placebo subjects, but the results were again not statistically significant (p=0.212).

Treatment-by-center interactions failed to achieve statistical significance for either percent reduction from baseline in PGTC seizures (p=0.250) or all seizures (p=0.781). The relative differences favoring TOP over placebo appeared consistent across centers (see Figure 3).

Efficacy summaries for each seizure type experienced during the double-blind phase favored TOP over placebo for myoclonic seizures (15.2% vs 5.5%) and absence seizures (-6.6% vs -16.1%). The number of subjects experiencing atypical absence, clonic, drop attack (including atonic), tonic, and other generalized seizures was too small (<8 in each treatment group) for meaningful comparisons (see Table 6b).

An analysis of treatment responders, defined as ≥50% reduction from baseline in seizure rate during the double-blind period, showed 54% responders in the TOP group vs 35% in the placebo (p=0.102) for PGTC seizures, and 40% of TOP subjects vs 20% for all seizures (p=0.061; see Table 10a). Treatment-by-center interactions were not statistically significant with respect to PGTC seizures (p=0.285) or all seizures (p=0.671). If, however, treatment response is defined as ≥75% reduction in PGTC seizure rate (*post-hoc* analysis), the difference between groups is statistically significant for both PGTC seizures (36% TOP subjects vs 15% placebo; p=0.040) and all seizures (30% TOP subjects vs 5% placebo; p=0.0005).

Another secondary efficacy measure, the global evaluation of seizure severity, did show statistical significance: 48% TOP subjects, compared to 33% placebo, reported subjective improvement (minimal, moderate, or marked) in seizure severity (p=0.026; see Table 11). Marked improvement was reported by 33% TOP subjects, but by none in the placebo group.

The reasons proposed by the sponsor to explain the lack of statistical significance in efficacy include (1) the imbalance in baseline PGTC seizure rate in favor of placebo (3 seizures/month for placebo vs 5 seizures/month for TOP); and (2) the higher number of placebo patients, compared to TOP, who reported efficacy-related results as safety assessments (3 placebo vs 1 TOP subject prematurely discontinued study medication because of aggravated convulsions). "Because of these efficacy-related discontinuations, the last-observation-carried-forward approach, which implicitly assumes uninformative censoring, becomes a more conservative approach as it may be somewhat biased against TOP" (v 39/168, p 103). However, the latter point would seem rather to favor the treatment arm.

Because of the imbalance in baseline PGTC seizure rate for the two groups, an additional analysis was conducted that included baseline PGTC seizure rate as a covariate. Efficacy variables considered included the percent reduction from baseline in PGTC seizure rate during the double-blind phase and percent responders based on ≥50% reduction in PGTC seizure rate. For percent reduction in PGTC seizure rate, the rank-based analysis method was employed with baseline

PGTC seizure rate as a covariate. The analysis of responders used logistic regression, with treatment, center, and baseline PGTC seizure rate as terms. Though not imbalanced at baseline, additional covariates, such as age and sex, were also considered, but had no important effect on the treatment comparisons.

The only covariate found to be statistically significant ($p<0.05$) for either analysis was baseline seizure rate: for PGTC responders, $p=0.016$, indicating TOP was superior to placebo, while the covariate (baseline seizure rate) was significantly associated with response ($p=0.002$) but the interaction between treatment and covariate was not ($p=0.693$). With regard to percent reduction from baseline in PGTC seizure rate, the baseline PGTC seizure rate had a weaker relationship with response ($p=0.078$); neither the covariate nor the interaction was statistically significant (v 39/168, p 63).

Finally, patient mental status was assessed by means of a questionnaire, "Global Evaluation of Mental Status," completed by subjects or their legal guardian at the first and final visits of the double-blind phase, with responses scored on a scale from 0 (worsening of mental status) to 4 (marked improvement). Comparison of the two questionnaires shows that most patients in either treatment group recognized no change (see Table 22).

PHARMACOKINETIC DATA: Median average dosage during the double-blind phase (titration and stabilization) was 3.6 mg/kg/day for TOP subjects, and during the stabilization period 5.1 mg/kg/day. 30 (75%) placebo and 29 (73%) TOP subjects achieved their target dosage at some point in the study (see Tables 15a and 15b); 24 (60%) placebo and 25 (63%) TOP subjects completed stabilization at that dosage (see Table 16).

The mean TOP plasma concentration over the entire double-blind period (titration and stabilization) was 5.3 ug/ml (c 39/168, p 53). The greatest reduction in PGTC seizures and in all seizures was seen in the middle plasma TOP concentration stratus (5.01-<9.67 ug/ml); see Table 13. No significant correlation was detected between TOP plasma concentration and percent reduction in average monthly PGTC seizure rate ($p=0.382$) or in the total seizure rate ($p=0.263$).

A *mean* decrease in the plasma concentration of valproic acid (-26.4 ug/ml) was noted and, according to the sponsor, was "consistent with previous pharmacokinetic data" ($p=0.189$) and "not in a direction that would be expected to favor TOP in efficacy comparisons" (v 39/168, p 65). This decrease, however, was effected by values from a single patient (discussed with Dr. Iftekar Mahmood, FDA Biopharm). Current labeling states that concomitant VPA concentration show no change. Mean changes from baseline in plasma concentrations of other concomitant AEDs were small and not statistically significant between TOP and placebo patients (see Table 12).

SUBGROUP ANALYSES: The ratio of male-to-female subjects was relatively close in both the drug-treated and placebo groups; see the demographics in Table 6b. Crude percentage rates were not provided in the NDA comparing the two groups in terms of median seizure reduction. However, no differences with regard to effectiveness or safety issues were noted for gender or age, according to a phone conversation with the sponsor on 2/10/98 (Catherine Glenkowski , covering for Michael Kaufman, Joe Ward [medical writer], and Judy Smith [statistician]).

Racial representation was sparse, and no conclusions can therefore be reached about the effect of TOP on groups other than Caucasian. There was only 1 black and, aside from whites, no other racial groups were represented.

Even pooling the pediatric populations of both YTC and YTCE would not yield an evaluable subgroup sufficiently large, by FDA traditional standards, to assess TOP's efficacy . However, case can be made to support such an indication, but on a much lower standard of evidence. See the summary below.

(4) Summary of PGTC Trials

There are two trials for primary generalized epilepsy, one highly significant (YTC) and the